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1/77

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1.	Your reference	**4-32634P1**
2.	Patent application number *(The Patent Office will fill in this part)*	0220581.3 — 04 SEP 2002
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	**NOVARTIS AG** **LICHTSTRASSE 35** **4056 BASEL** **SWITZERLAND**
	Patent ADP number *(if you know it)*	07125487005
	If the applicant is a corporate body, give the country/state of its incorporation	**SWITZERLAND**
4.	Title of invention	**Organic compound**
5.	Name of your agent *(If you have one)*	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	**B.A. YORKE & CO.** **CHARTERED PATENT AGENTS** **COOMB HOUSE, 7 ST. JOHN'S ROAD** **ISLEWORTH** **MIDDLESEX TW7 6NH**
	Patents ADP number *(if you know it)*	**1800001**
6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country / Priority application number *(if you know it)* / Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application / Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	**Yes**

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Continuation sheets of this form	
Description	15
Claim(s)	3
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10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	ONE
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature B. A. Yorke & Co. Date **B.A. Yorke & Co.** **04 September 2002**

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. E. Cheetham
020 8560 5847

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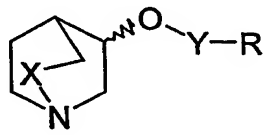
DUPLICATE

Organic compound

The present invention relates to novel 1-aza-bicycloalkyl derivatives, to processes for their production, their use as pharmaceuticals and to pharmaceutical compositions comprising them.

More particularly the present invention provides in a first aspect, a compound of formula I

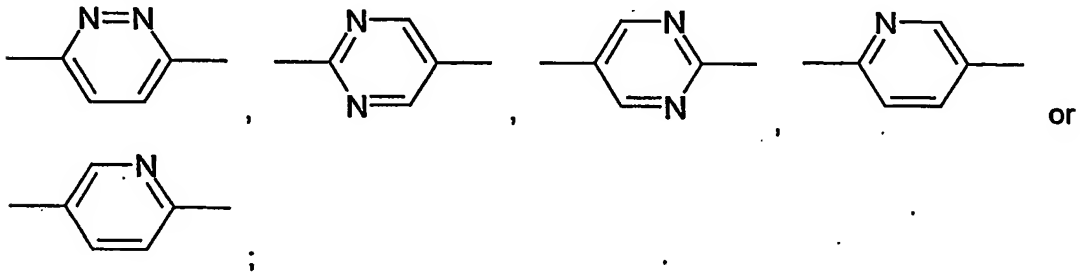


(I)

wherein

X is CH_2 or a single bond;

Y is a group of formula



;

R is a substituted or unsubstituted C_5-C_{10}aryl or substituted or unsubstituted hetero-C_5-C_{10}aryl, $N(R^1)(R^4)$, or $N(R^2)(CHR^3R^4)$;

each of R^1, R^2 and R^3 is independently H, C_1-C_4alkyl, or CF_3;

R^4 is a substituted or unsubstituted C_5-C_{10}aryl or substituted or unsubstituted hetero-C_5-C_{10}aryl;

in free base or acid addition salt form.

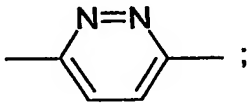
C_5-C_{10}aryl or hetero-C_5-C_{10}aryl residues are to be understood as aromatic residues optionally substituted by one or more substituents selected from halogen, e.g. F, Cl, Br, I; CN, or C_1-C_2alkyl which again can be unsubstituted or substituted by halogen; e.g. trifluoromethyl; or C_1-C_4alkoxy, or condensed, e.g. to a benzo[1,3]dioxole or 2,3-dihydrobenzo[1,4]dioxine and/or to a further heterocyclic ring. Hetero-C_5-C_{10}aryl is an aromatic heterocyclic system comprising one, two or three hetero atoms selected from N, O, S, e.g. a 5 or 7 membered aromatic heterocyclic residue optionally condensed, e.g. to 1 or 2 phenyl rings and/or to a

further heterocyclic ring. Examples of C_5-C_{10}aryl or hetero-C_5-C_{10}aryl residues as mentioned above include phenyl, naphthyl, thiophenyl and isobenzofuranyl.

On account of the asymmetrical carbon atom(s) present in the compounds of formula I and their salts, the compounds may exist in optically active form or in form of mixtures of optical isomers, e.g. in form of racemic mixtures. All optical isomers and their mixtures including the racemic mixtures are part of the present invention.

In formula I the following significances are preferred independently, collectively or in any combination or sub-combination:

(a) X is CH_2;

(b) Y is  ;

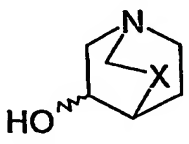
(c) R is 1- isobenzofuranyl or substituted or unsubstituted phenyl, e.g. monosubstituted by a chlorine or fluorine in position 2, 3 or 4, CF_3 in position 2 or 3, methoxy in position 2; trifluoromethoxy in position 3; benzo[1,3]-dioxole; 2,3-dihydrobenzo[1,4]-dioxine; cyano; or disubstituted, e.g. by a fluorine in position 2 and 5, 3 and 5 or chlorine in position 2 and fluorine in position 6.

In addition to the foregoing the present invention also provides a process for the production of a compound of formula I, which process comprises the step of

reacting a compound of formula II

z-Y-R (II);

wherein Y and R are as defined above and z is a leaving group, e.g. F, Cl, Br, I or OSO_2CF_3, with a compound of formula III

 (III)

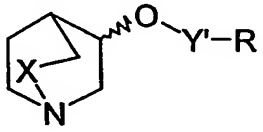
wherein X is as defined above,

and recovering the so obtained compound of formula I in free base or acid addition salt form.

The reaction may be carried out in accordance with standard procedures, for example as illustrated in the Examples.

Compounds of formula II are known or may be prepared from corresponding known compounds, e.g. as described in the Examples, e.g. in analogy to Coates WJ, McKillop A (1992) Synthesis 334-342. The compounds of formula III are known.

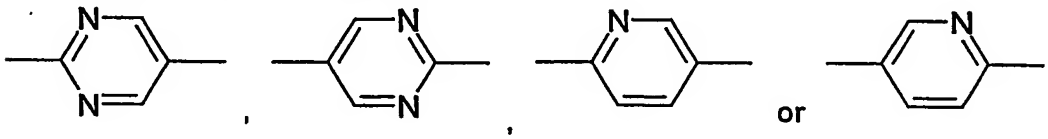
Alternatively, the compounds of formula I'



(I')

wherein

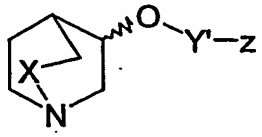
X and R are as defined above and Y' is



, can be

produced by a process comprising the step of

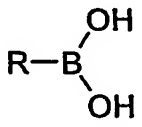
reacting a compound of formula IV



(IV);

wherein Y', z and X are as defined above,

with a compound of formula V



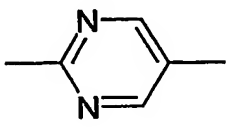
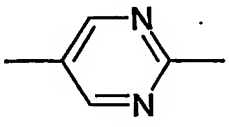
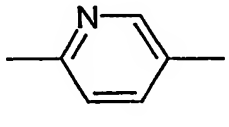
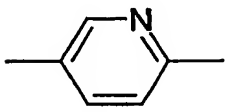
(V)

wherein R is as defined above,

and recovering the so obtained compound of formula I' in free base or acid addition salt form.

Compounds of formula IV are known or may be prepared from corresponding known compounds, e.g. as described in Example 17, e.g. by reacting compounds of formula III with compounds of formula II';

z-Y'-OH (II');

wherein Y' is  ,  ,  or  and z is as described above.

Compounds of formula V (e.g. unsubstituted or substituted phenylboronic acids) are known or may be prepared from corresponding known compounds.
Working up the reaction mixtures according to the above processes and purification of the compounds thus obtained may be carried out in accordance to known procedures.

Acid addition salts may be produced from the free bases in known manner, and vice-versa. Suitable acid addition salts for use in accordance with the present invention include for example the hydrochloride.

Compounds of formula I in optically pure form can be obtained from the corresponding racemates according to well-known procedures, e.g. HPLC with chiral matrix. Alternatively, optically pure starting materials can be used.

The compounds of the invention and their pharmaceutically acceptable acid addition salts, hereinafter referred to as agents of the invention, exhibit valuable pharmacological properties when tested in vitro and in animals, and are therefore useful as pharmaceuticals.

In particular, the agents of the invention are α7 nicotinic acetylcholine receptor (nAChR) agonists.

In functional assays, the agents of the invention display high affinity at the α7 nAChR as shown in the following tests:

a) A functional assay for affinity at the α7 nAChR is carried out with a rat pituitary cell line stably expressing the α7 nAChR. As a read out, the calcium influx upon stimulation of the receptor is used. In this assay, agents of the invention exhibit pEC_{50} values of about 5 to about 8.

b) To assess the activity of the agents of the invention on the human neuronal nAChR α 4β2, a similar functional assay is carried out using a human epithelial cell line stable expressing the human α4β2 subtype. In this assay, agents of the invention show selectivity for the α7 nAChR subtypes.

c) To assess the activity of the compounds of the invention on the "ganglionic subtype" and the muscle type of nicotinic receptor, similar functional assays as described under a) are carried out with a human epithelial cell line stably expressing the human ganglionic subtype or a cell line endogenously expressing the human muscle type of nicotinic receptors. In these assays, agents of the invention display no or little activity on the ganglionic and muscle type of nicotinic receptor subtypes.

In the model of mice showing sensory gating deficit (DBA/2-mice) described by S. Leonard et al. in Schizophrenia Bulletin 22, 431-445 (1996), the agents of the invention induce significant sensory gating at concentrations of about 10 to about 40 μM.

The agents of the invention are therefore useful for the prevention and treatment of psychotic disorders such as schizophrenia, mania, depression and anxiety, and for the prevention and treatment of neurodegenerative disorders such as senile dementia, Alzheimer's disease and other intellectual impairment disorders, such as attention deficit hyperactivity disorders (ADHD); Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis, multiple sclerosis, epilepsy, convulsions, Tourette syndrome, OCD (obsessive compulsive disorder), neuropathic, postoperative and inflammatory pain, phantom limb pain, cognition, smoking cessation, memory deficits and dysfunction, learning deficit, panic disorders, narcolepsy, nociception, AIDS dementia, senile dementia, autism, tardive dyskinesia, social phobia, pseudodementia. The usefulness of α7 nAChR agonists in neurodegeneration is documented in the literature, e.g. in Wang et al., J. biol. Chem. 275, 5626-5632 (2000).

For the above indications the appropriate dosage of the agents of the invention will, of course, vary depending upon, for example, the host, the mode of administration and the nature and severity of the condition being treated as well as the relative potency of the particular an agent of the invention employed. For example, the amount of active agent required may be determined on the basis of known in vitro and in vivo techniques, determining how long a particular active agent concentration in the blood plasma remains at an acceptable level for a therapeutic effect. In general, satisfactory results in animals are indicated to be obtained at daily dosages of from about 0.01 to about 20.0 mg/kg p.o. In humans, an indicated daily dosage is in the range of from about 0.7 to about 1400 mg/day p.o., e.g. from about 50 to 200 mg (70 kg man), conveniently administered once or in divided doses up to 4 x per day or in sustained release form. Oral dosage forms accordingly suitably comprise from about 1.75 or 2.0 to about 700 or 1400 mg of an agent of the invention admixed with an appropriate pharmaceutically acceptable diluent or carrier therefor.

Examples for compositions comprising an agent of the invention include, e.g. a solid dispersion, an aqueous solution, e.g. containing a solubilising agent, a microemulsion and a suspension of, e.g. a hydrochloride salt of a compound of formula I in the range of from 0.1 to 1 %, e.g. 0.5 %. The composition may be buffered to a pH in the range of, e.g. from 3.5 to 9.5, e.g. to pH 4.5, by a suitable buffer.

The agents of the invention are also useful as research chemicals.

For use according to the invention, the agent of the invention may be administered as single active agent or in combination with other active agents, in any usual manner, e.g. orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injection solutions or suspensions.

The pharmaceutical compositions for separate administration of the combination partners and for the administration in a fixed combination, i.e. a single galenical composition comprising at least two combination partners, according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals, including man, comprising a therapeutically effective amount of at least one pharmacologically active combination partner alone or in combination

with one or more pharmaceutically acceptable carries, especially suitable for enteral or parenteral application.

Pharmaceutical compositions contain, for example, from about 0.1 % to about 99.9 %, preferably from about 20 % to about 60 %, of the active ingredients. Pharmaceutical preparations for the combination therapy for enteral or parenteral administration are, for example, those in unit dosage forms, such as sugar-coated tablets, tablets, capsules or suppositories, and furthermore ampoules. If not indicated otherwise, these are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. It will be appreciated that the unit content of a combination partner contained in an individual dose of each dosage form need not in itself constitute an effective amount since the necessary effective amount can be reached by administration of a plurality of dosage units.

In particular, a therapeutically effective amount of each of the combination partners may be administered simultaneously or sequentially and in any order, and the components may be administered separately or as a fixed combination. For example, the method of delay of progression or treatment of a proliferative disease according to the invention may comprise (i) administration of the combination partner (a) in free or pharmaceutically acceptable salt form and (ii) administration of a combination partner (b) in free or pharmaceutically acceptable salt form, simultaneously or sequentially in any order, in jointly therapeutically effective amounts, preferably in synergistically effective amounts, e.g. in daily dosages corresponding to the amounts described herein. The individual combination partners can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. Furthermore, the term administering also encompasses the use of a pro-drug of a combination partner that convert *in vivo* to the combination partner as such. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

The effective dosage of each of the combination partners employed may vary depending on the particular compound or pharmaceutical composition employed, the mode of administration, the condition being treated, the severity of the condition being treated. Thus, the dosage regimen is selected in accordance with a variety of factors including the route of

administration and the renal and hepatic function of the patient. A physician, clinician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the single active ingredients required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of the active ingredients within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the active ingredients' availability to target sites. In general, satisfactory results in animals are indicated to be obtained at daily dosages of from about 0.01 to about 20.0 mg/kg p.o. In humans, an indicated daily dosage is in the range of from about 0.7 to about 1400 mg/day p.o., e.g. from about 50 to 200 mg (70 kg man), conveniently administered once or in divided doses up to 4 x per day or in sustained release form. Oral dosage forms accordingly suitably comprise from about 1.75 or 2.0 to about 700 or 1400 mg.

In accordance with the foregoing, the present invention also provides:

(1) An agent of the invention for use as an alpha-7 receptor agonist, for example for use in any of the particular indications hereinbefore set forth;

(2) A pharmaceutical composition comprising an agent of the invention as active ingredient together with a pharmaceutically acceptable diluent or carrier therefore.

(2') A pharmaceutical composition for the treatment or prevention of a disease or condition in which alpha-7 receptor activation plays a role or is implicated comprising an agent of the invention and a carrier.

(3) A method for the treatment of any of particular indication hereinbefore set forth in a subject in need thereof which comprises administering an effective amount of an agent of the invention;

(3') A method for treating or preventing a disease or condition in which the alpha-7 receptor activation plays a role or is implicated comprising administering to a mammal in need thereof a therapeutically effective amount of an agent of the invention.

(4) The use of an agent of the invention for the manufacture of a medicament for the treatment or prevention of a disease or condition in which the alpha-7 receptor activation plays a role or is implicated;

(5) A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a alpha-7 agonist, e.g. an agent of the invention and a second drug substance, said second drug substance being for example for use in any of the particular indications hereinbefore set forth.

(6) A combination comprising a therapeutically effective amount of a alpha-7 agonist agonist, e.g. an agent of the invention and a second drug substance, said second drug substance being for example for use in any of the particular indications hereinbefore set forth.

The preferred compounds of formula I for use in accordance with the invention are those of Examples 2, 18 and 30 which have a pEC_{50} value between 7 and 8.

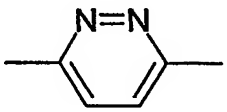
Abbreviations used in the examples:

AcOEt	ethyl acetate
aq.	aqueous
DEAD	diethylazodicarboxylate
DMF	dimethylformamide
EtOH	ethanol
FC	flash chromatography
HV	high vacuum
MeOH	MeOH
RP-HPLC	reversed-phase high performance liquid chromatography
rt	room temperature
rac.	racemate
soln.	solution
TFA	trifluoroacetic acid
THF	tetrahydrofuran

The following Examples illustrate the invention.

Example 1: Preparation of (*rac.*)-3-[6-(4-fluorophenyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane

A solution of (*rac.*)-3-quinuclidinol (0.007 mole) in dry THF under nitrogen is treated with sodium hydride (60% in mineral oil; 1.1 equiv.). After 1 hr at room temperature, a solution of 3-Chloro-6-(4-fluoro-phenyl)pyridazine (1.0 equiv.) in THF (30 ml) is added, and the reaction mixture heated to reflux for 6 hrs. After cooling to room temperature, the THF is evaporated and the residue dissolved in ethyl acetate (100 ml) and then washed with water (3 × 20 ml), followed by sodium chloride solution (20 ml). The ethyl acetate is dried over anhydrous magnesium sulfate, filtered and evaporated to dryness, and the residual oil purified by silica gel column chromatography (eluent: ethyl acetate-methanol-triethylamine (50:10:2) to afford (*rac.*)-3-[6-(4-fluorophenyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane as a colourless solid. 1H-NMR (400 MHz, $CDCl_3$): δ = 8.00 (*m*, 2H), 7.75 (*d*, 1H), 7.17 (m, 2H), 7.1 (d, 1H), 5.35 (m, 1H), 3.5 (m, 1H), 2.99-2.83 (m, 5H), 2.32 (m, 1H), 1.98 (m, 1H), 1.76-1.68 (m, 2H), 1.46 (m, 1H).

The following compounds of formula I wherein Y is  can be prepared in analogy to Example 1:

Ex.	stereo-chem.	X	R	HPLC rt (min)	$[\alpha]_D^{rt}$	mp. °C (salt)	$M+H^+$
2	(3R,4S)	bond	phenyl	5.7	-23.5° (0.1% MeOH)	143-145 (no salt)	268
3	(3S,4R)	bond	phenyl	5.7	-26.5° (0.1% MeOH)	145-147 (no salt)	268
4	(S)	CH_2	phenyl	5.2	-32.5° (0.5% MeOH)	128-130 (no salt)	282.2
5	(R)	o-NO_2	4-chloro-phenyl	6.2	+29.0° (0.1% MeOH)	175-177 (no salt)	316.2
6	(R)	CH_2	3-chloro-phenyl	6.2	+38.5° (0.1% MeOH)	98-100 (no salt)	316.2

7	*rac.*	CH_2	2-methoxy-phenyl	5.5	N/A	125-128 (no salt)	312.4
8	(R)	CH_2	4-trifluoromethyl-phenyl	7.0	+28 (0.1% MeOH)	172-175 (no salt)	350.5
9	(R)	CH_2	2-fluoro-phenyl	5.6	+23.5° (0.1% MeOH)	110-113 (no salt)	300.2
10	(R)	CH_2	2-chloro-phenyl	5.7	+29.5° (0.1% MeOH)	85-87 (no salt)	316.2
11	(R)	CH_2	4-fluoro-phenyl	5.7	+39.5° (0.1% MeOH)	146-149 (no salt)	300.2
12	(R)	CH_2	3-fluoro-phenyl	5.5	+31.5° (0.1% MeOH)	118-121 (no salt)	300.2
13	(R)	CH_2	3,4-dichloro-phenyl	7.3	+29.5° (0.1% MeOH)	173-175 (no salt)	350.2
14	(R)	CH_2	3-trifluoromethyl-phenyl	6.9	+23.0° (0.1% MeOH)	112-115 (no salt)	350.3
15	(R)	CH_2	3,5-dichloro-phenyl	7.3	+31.0° (0.1% MeOH)	127-130 (no salt)	350.2
16	(R)	CH_2	1-isobenzofuranyl	6.8	+29.0 (0.1% MeOH)	193-195° (no salt)	321.38

Example 17: Preparation of (*rac.*)-3-(5-Phenyl-pyrimidin-2-yloxy)-1-aza-bicyclo[2.2.2]octane

5-Bromo-2-hydroxy-pyrimidine (400 mg, 2.29 mmol), (*rac.*)-3-quinuclidinol (432 mg, 3.36 mmol) and triphenylphosphine (890 mg, 3.40 mmol) are dissolved in THF (25 ml). After stirring for 10' at –10°C, a solution of DEAD (522 µl, 3.36 mmol) in THF (20 ml) is added dropwise. The reaction mixture is allowed to warm to rt and is stirred for 16h at rt. The reaction mixture is evaporated to give an orange semi-solid (2.50 g), which is triturated with AcOEt and filtered to give (*rac.*)-3-(5-bromo-pyrimidin-2-yloxy)-1-aza-bicyclo[2.2.2]-octane as a white solid. The filtrate is purified by FC (silica gel, eluents: AcOEt/MeOH 9:1, then

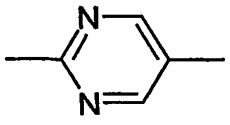
AcOEt/MeOH/NEt_3 70:27:3). (*rac.*)-3-(5-Bromo-pyrimidin-2-yloxy)-1-aza-bicyclo[2.2.2]octane (150 mg, 0.53 mmol), phenylboronic acid (66 mg, 0.54 mmol) and tetrakis(triphenylphosphine)palladium are dissolved in toluene:EtOH 9:1 (15 ml). Na_2CO_3 (225 mg, 2.12 mmol) is dissolved in water (1.5 ml) and added to the reaction mixture, which is heated at 90°C for 20h. After cooling to rt, it is filtered over celite; the toluene layer is separated and washed with brine. The aq. layers are re-extracted with AcOEt, the combined organic extracts are dried over $MgSO_4$, filtered and the filtrate is evaporated to give a light yellow gum (195 mg) that is purified by FC (silica gel, eluents: AcOEt/MeOH 9:1, then AcOEt/MeOH/NEt_3 70:27:3) to give a white solid which still contains starting material. A second purification is done by RP-HPLC (Phenomenex RP18 column, gradient 0.08% aq. HCOOH/CH_3CN 95:5 → CH_3CN in 20') to give (*rac*)-3-(5-phenyl-pyrimidin-2-yloxy)-1-aza-bicyclo[2.2.2]octane as its formate salt.

1H-NMR (400 MHz, CDCl3): δ = 8.74 (*s*, 2H), 8.51 (*s*, 1H), 7.59-7.45 (*m*, 5H), 5.35-5.28 (*m*, 1H), 3.82-3.74 (*m*, 1H), 3.70-3.14 (*m*, 5H), 2.62-2.54 (*m*, 1H), 2.53-2.42 (*m*, 1H), 2.13-1.91 (*m*, 2H), 1.87-1.76 (*m*, 1H); HPLC rt (min): 5.4; mp °C: 108-114; $M+H^+$ 282.2.

Example 18: Preparation of (*R*)-3-(5-Phenyl-pyrimidin-2-yloxy)-1-aza-bicyclo[2.2.2]octane

5-Bromo-2-chloro-pyrimidine (400 mg, 2.03 mmol), phenylboronic acid (253 mg, 2.07 mmol) and tetrakis(triphenylphosphine)palladium (118 mg, 0.102 mmol) are dissolved in toluene/EtOH 9:1 (50 ml). Na_2CO_3 (861 mg, 8.12 mmol) is dissolved in water (4 ml) and added to the reaction mixture. The mixture is stirred at 90°C for 19h, cooled to rt and filtered over celite. The toluene layer is separated and washed with brine. The aq. layers are re-extracted with AcOEt; the combined organic extracts are dried over $MgSO_4$ and filtered. The filtrate is evaporated to give a yellow solid (503 mg), which is purified by FC (silica gel, eluents cyclohexane and AcOEt/cyclohexane 1:9) to give 2-chloro-5-phenyl-pyrimidine. (*R*)-3-quinuclidinol (478 mg, 3.76 mmol) is added to a suspension of NaH (164 mg of a 60% dispersion in mineral oil, 4.09 mmol) in DMF (10 ml). The mixture is stirred for 1h at rt. 2-Chloro-5-phenyl-pyrimidine (177 mg, 0.93 mmol) is added and the mixture is heated for 3.5 h at 90°C. The reaction mixture is diluted with toluene and washed with 1M aq. NaOH solution and brine. The aq. layers are re-extracted with toluene (3x). The combined organic extracts are dried over $MgSO_4$ and filtered. The filtrate is evaporated to give a yellow solid (310 mg), which is purified by FC (silica gel, eluents: AcOEt, then AcOEt/MeOH/NEt_3 80:18:2). A second purification is done by RP-HPLC (Phenomenex RP18 column, gradient 0.08% aq.

HCOOH → 0.08% aq. HCOOH/CH3CN 80:20 in 10', → CH_3CN in 15') to give (*R*)-3-(5-phenyl-pyrimidin-2-yloxy)-1-aza-bicyclo[2.2.2]-octane as its formate salt.
1H-NMR (400 MHz, DMSO): δ = 8.95 (*s*, 2H), 8.26 (*s*, 1H), 7.79-7.71 (*m*, 2H), 7.55-7.42 (*m*, 3H), 5.13-5.06 (*m*, 1H), 3.46-3.36 (*m*, 1H), 2.99-2.75 (*m*, 5H), 2.26-2.20 (*m*, 1H), 1.99-1.88-2.42 (*m*, 1H), 1.81-1.63 (*m*, 2H), 1.56-1.45 (*m*, 1H), HPLC rt (min): 5.4; mp °C: 108-110; $[\alpha]_D^{rt}$ +8.6 (1.03, MeOH), M+H^+ 282.2.

The following compounds of formula I wherein Y is  can be prepared in analogy to Example 17 or 18:

Ex.	stereo -chem.	X	R	HPLC rt (min)	$[\alpha]_D^{rt}$	mp. °C (salt)	M+H^+
19	(S)	CH_2	phenyl	5.6	-31.0° (0.95% MeOH)	126-129 (no salt)	282.2
20	*rac.*	CH_2	2-fluoro-phenyl	5.9	N/A	87-93 (no salt)	300.2
21	*rac.*	CH_2	3-chloro-phenyl	6.6	N/A	163-165 (no salt)	316.2
22	*rac.*	CH_2	3,4-dichloro-phenyl	3.6	N/A	182-184 (no salt)	350.1
23	*rac.*	CH_2	2,4-dichloro-phenyl	3.6	N/A	N/A (oil) (HCl salt)	350.1
24	*rac.*	CH_2	3,5-dichloro-phenyl	3.7	N/A	183-184 (no salt)	350.1
25	*rac.*	CH_2	3-cyano-phenyl	3.5	N/A	189 (no salt)	307.2
26	*rac.*	CH_2	3-trifluoromethyl-phenyl	3.5	N/A	158-159 (no salt)	350.2

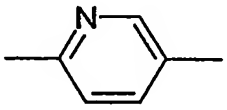
Example 27: Preparation of *rac*-3-(6-Phenyl-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]-octane

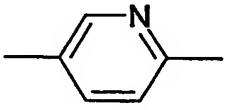
Bromine (1.1 ml, 21.41 mmol) is slowly added to a soln. of 2-amino-5-chloropyridine (1.00 g, 7.78 mmol) in 47% aq. HBr (6 ml) at –10°C. An aq. soln. of $NaNO_2$ (1.57 g, 22.75 mmol) is slowly added. The mixture is stirred for 1h at –10 to –5°C, then for 1h at 5°C. The mixture is neutralised with 5M aq. NaOH soln. maintaining the temperature below 25°C. The orange precipitate is filtered, washed with water and dried in HV to give 2-bromo-5-chloropyridine.

2-Bromo-5-chloropyridine (503 mg, 2.61 mmol), phenylboronic acid (325 mg, 2.67 mmol) and tetrakis(triphenylphosphine)palladium (152 mg, 0.13 mmol) are dissolved in toluene:EtOH 9:1 (65 ml). Na_2CO_3 (1.11 g, 10.47 mmol) is dissolved in water (5.2 ml) and added to the reaction mixture. The mixture is stirred at 90°C for 19h, cooled to room temperature and filtered over celite. The toluene layer is separated and washed with brine. The aq. layers are extracted with AcOEt. The combined organic extracts are dried over $MgSO_4$ and filtered. The filtrate is evaporated to give a brown solid (733 mg), which is purified by FC (silica gel, eluents cyclohexane and AcOEt/cyclohexane 1:4) to give 5-chloro-2-phenyl-pyridine.

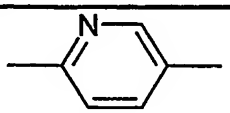
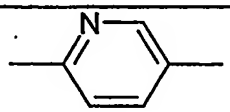
(*rac.*)-3-Quinuclidinol (653 mg, 5.13 mmol) is added to a suspension of NaH (224 mg of a 60% dispersion in mineral oil, 5.59 mmol) in DMF (15 ml). The mixture is stirred for 1h at rt. 5-Chloro-2-phenyl-pyridine (240 mg, 1.27 mmol) is added and the mixture is heated for 4.5 h at 90°C, then for 12h at rt. The reaction mixture is diluted with toluene and washed with 1M aq. NaOH soln. and brine. The aq. layers are re-extracted with toluene (3x). The combined organic extracts are dried over $MgSO_4$ and filtered. The filtrate is evaporated to give a brown oil (338 mg) which is purified by FC (silica gel, eluents: AcOEt, then AcOEt/MeOH/NEt_3 50:10:2) to give *rac*-3-(6-phenyl-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]-octane.

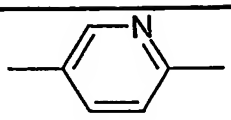
1H-NMR (400 MHz, $CDCl_3$): δ = 8.41-8.37 (*m*, 1H), 7.99-7.94 (*m*, 2H), 7.72-7.66 (*m*, 1H), 7.52-7.46 (*m*, 2H), 7.44-7.38 (*m*, 1H), 7.32-7.23 (*m*, 1H), 4.52-4.46 (*m*, 1H), 3.42-3.32 (*m*, 1H), 3.10-2.80 (*m*, 5H), 2.27-2.21 (*m*, 1H), 2.10-1.96 (*m*, 1H), 1.87-1.77 (*m*, 1H), 1.68-1.58 (*m*, 1H), 1.53-1.42 (*m*, 1H), HPLC rt (min): 4.9; mp °C: 75-78; $M+H^+$ 281.2.

The following compounds of formula I wherein Y is,  , or



can be prepared in analogy to Example 20:

Ex.	stereo -chem.	X	Y	R	HPLC rt (min)	$[\alpha]_D^{rt}$	mp. °C (salt)	$M+H^+$
28	rac.	CH_2		phenyl	6.8	N/A	75-80 (no salt)	281.2
29	(R)	CH_2		phenyl	5.4	+34.6° (1.0% MeOH)	78-81 (no salt)	281.2

30	(R)	CH_2		phenyl	4.2	-19.1 (0.5% MeOH)	226-236 (HCl salt)	281.2

HPLC conditions:

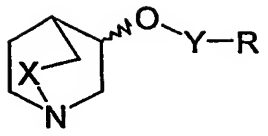
for Examples 1-21, 27, 28: Column Phenomenex Luna or Kingsorb C18, 30x4.6 mm, 3 μM. Gradient (A {H_2O+ 0.08% HCOOH} B CH_3CN): 0 to 5min: A:B 100:0 to 80:20, 5 to 10 min: 80:20 to 0:100, flow 3.0 ml/min.

for Examples 22-26: Column Waters Xterra MS C18, 50x2.1 mm, 2.5 μM. Gradient (A:{H_2O+0.02%TFA}, B:{CH_3CN+0.02%TFA}): 0 to 2 min: A:B 90:10 to 5:95; 2 to 4 min: 5:95, 4 to 5.5 min 5:95 to 10:90, 5.5 to 6 min: 10:90 to 90:10, 6 to 7 min: 90:10, flow 0.35 ml/min.

for Examples 29, 30: Column Waters Xterra MS C18, 150x2.1 mm, 3.5 μM. Gradient (A:{H_2O+0.02%TFA}, B:{CH_3CN+0.02%TFA}): 0 to 3 min: A:B 90:10 to 10:90; 3 to 8 min: 10:90, 8 to 9 min: 10:90 to 90:10, 9 to 15 min: 90:10, flow 0.35 ml/min.

Claims:

1. A compound of formula I

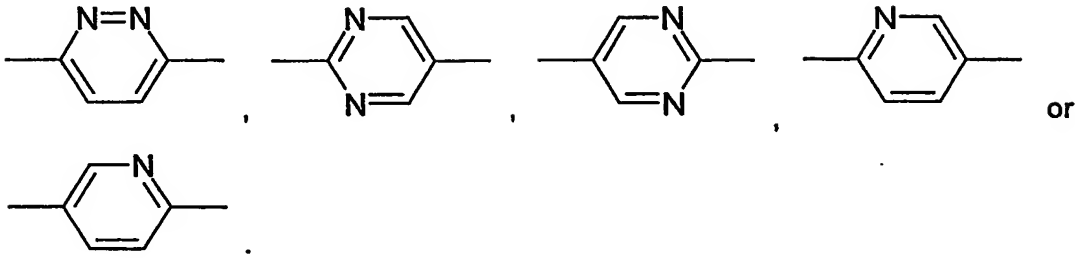


(I)

wherein

X is CH_2 or a single bond;

Y is a group of formula



;

R is a substituted or unsubstituted C_5-C_{10}aryl or substituted or unsubstituted hetero-C_5-C_{10}aryl, $N(R^1)(R^4)$, or $N(R^2)(CHR^3R^4)$;

each of R^1, R^2 and R^3 is independently H, C_1-C_4alkyl, or CF_3;

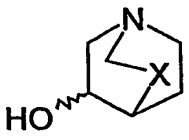
R^4 is a substituted or unsubstituted C_5-C_{10}aryl or substituted or unsubstituted hetero-C_5-C_{10}aryl;

in free base or acid addition salt form.

2. A process for the preparation of a compound of formula I as defined in claim 1, or a salt thereof, which comprises the step of reacting a compound of formula II

z-Y-R (II)

wherein Y and R are as defined in claim 1 and z is a leaving group with a compound of formula III



(III)

wherein X is as defined in claim 1,

and recovering the so obtained compound of formula I in free base or acid addition salt form.

3. The compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

4. The compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use in the prevention and treatment of psychotic and neurodegenerative disorders.

5. A pharmaceutical composition comprising a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

6. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, as a pharmaceutical for the prevention and the treatment of psychotic and neurodegenerative disorders.

7. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the prevention and treatment of psychotic and neurodegenerative disorders.

8. A method for the prevention and treatment of psychotic and neurodegenerative disorders, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form.

9. A compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use in the treatment or prevention of a disease or condition in which α7 nAChR activation plays a role or is implicated.

10. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, as a pharmaceutical for the treatment or prevention of a disease or condition in which α7 nAChR activation plays a role or is implicated.

11. A method for treating or preventing a disease or condition in which α7 nAChR activation plays a role or is implicated, in a subject in need of such treatment, which comprises

administering to such subject a therapeutically effective amount of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form.